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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,377	07/10/2001	Keith D. Allen	R-365	8328

26619 7590 07/27/2005

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EXAMINER
TON, THAIAN N

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/903,377	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *31-34,38 and 40-44* is/are pending in the application.

4a) Of the above claim(s) *44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-34,38 and 40-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.60

DETAILED ACTION

Applicants' Amendment and Response, filed 5/9/05, has been entered. Claims 1-30, 35-37 and 39 are cancelled. Claims 31-32, 34, 38, 42 and 43 have been amended; claim 44 is added; claim 44 is withdrawn; claims 31-34, 38 and 40-43 are under current examination.

Specification

The amendment filed 5/9/05 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. §132 states that no amendment shall introduce new matter into the disclosure of the invention.

Applicant has amended the specification at page 11, paragraphs 4-5, to incorporate US Provisional Application 60/084,194. This reference is not considered new matter because the original specification incorporated USSN 08/971,310 by reference, which was converted to the Provisional Application 60/084194. However, the additional references are considered new matter. The references include a second provisional application (60/084,949), a utility application claiming priority to the two provisional applications (09/193,834) and a second utility application that is a continuation of the first utility application (09/885,816; published as US Patent 6,815,185). There is no evidence that these newly referenced applications were contemplated as being part of the original specification as an incorporation by reference. The reference to "U.S. Patent no. 6,815,185 issued November 9, 2004,

which is based on U.S. Patent Application No. 09/885,816, filed June 19, 2001, which is a continuation of U.S. Application No. 09/193,834, filed November 17, 1998, now abandoned, which claims priority to provisional application no. 60/084,949, filed on May 11, 1998, and provisional application no. 60/084,194, the disclosure of provisional application no. 60/084,194" should be replaced with "US Patent Application No. 08/971,310, which was converted to provisional application no. 60/084194". The other applications should not be included.

Election/Restrictions

Newly submitted claim 44 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The claim is directed to a method of identifying an agent capable of modulating activity of a chemokine receptor 9A gene or chemokine receptor 9A gene expression product. The originally presented invention is directed to transgenic mice whose genome comprise a null chemokine receptor 9A allele, methods of producing such mice, targeting constructs and cells isolated from said mice. Thus, the mice of the originally presented invention are distinct from the invention of claim 44, as these mice can allegedly be used in different methods. For example, these mice can allegedly be used as models of disease or condition.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original

presentation for prosecution on the merits. Accordingly, claim 44 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections – 35 USC §101 & 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31-34, 38 and 40-43 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. This rejection is maintained for reasons of record advanced in the prior Office actions.

Applicants traverse the prior rejection, point to the MPEP to support that the Office should presume a statement of utility made by application is true, point that rejections under 35 U.S.C. 101 have been rarely sustained by federal courts, and that the burden is on the Examiner to show that one of ordinary skill in the art would find the asserted utility to be false. See pp. 5-6 of the Response. Applicants argue that the present invention has a well-established utility because one of

ordinary skill in the art would "immediately appreciate why" knockout mice are useful, namely, because the mice have an inherent and well-established utility of defining the function and role of the disrupted target gene, regardless of whether the inventor has described any specific phenotypes, characterizations or properties of the claimed knockout mice. Applicants point to the NIH to support that knockout mice represent a critical tool in studying gene function. See pp. 6-7 of the Response. Finally, Applicants argue that knockout mice are so well-accepted as tools for determining gene function, that various individuals have proposed creating knockout mice for all genes. See p. 7 of the Response. Applicants argue that which respect to the claims drawn to transgenic mice having a null allele, Applicants provide Austin *et al.*, who state that null-reporter alleles should be created, that they are an, "indispensable starting point for studying the function of every gene." Further, Applicants argue that research tools, such as the instantly claimed knockout mice, are patentable because they have a clear, specific and unquestionable utility, which is to analyze gene function. Applicants further argue that various authors provide support for the asserted utility of the claimed mice, for example, Alberts *et al.* provide teachings to show that knockout mice are "invaluable tools for investigating gene function," Genes VII states that knocking out of a gene is, "[A] powerful method to investigate directly the importance and function of the gene." See pp. 8-9 of the Response. Applicants further argue that the commercial use of the knockout mice has been clearly established because a

large pharmaceutical company has ordered the claimed transgenic mice, and that it cannot be reasonably argued that the claimed invention has no "real world use". Applicants submit that one of ordinary skill in the art would immediately recognize the utility of a knockout mouse in studying gene function, and that this utility is found to be specific or substantial. See p. 10 of the Response.

This is not persuasive. In the instant case, the claimed knockout mice lack utility for the reasons set forth in the previous Office actions. For example, knockout mice may not be capable of elucidating the function of the protein and may only provide a clue to a pathway the protein being knocked out is involved in. However, the contemplated utilities of using the instant mice to obtain a clue to a pathway is not a considered "substantial utility." Note that it was scientifically well-known to knock out a gene to determine its function or what will happen when the gene is not expressed. This is supported further by Applicants' response. However, scientific "utility" is not the same as "patentable utility" or a "well-established" utility. The MPEP and utility guidelines clearly set forth that a "well-established utility" must be specific, substantial and credible. At the time of filing, knockout mice were used for further research in the art. However, further research does not rise to the level of a "well-established utility" because such a utility is not substantial, specific or credible.

The asserted utility is not considered to be specific and substantial because the evidence of record has not provided a correlation between a disruption of a

chemokine receptor 9A allele and the phenotype of decreased performance on an accelerating rotarod, characterized by falling from an accelerating roatrod at lower speeds relative to a wild-type mouse; thus, the asserted utilities of the mice is not apparent. As stated previously, the instant specification fails to adequately demonstrate or teach that the response of the claimed transgenic mouse is due to decreased agility, coordination, or balance. The evidence and teachings of record fail to provide a nexus between a chemokine receptor 9A allele and any particular disease or disorder associated with it. Furthermore, neither the specification nor any evidence or teachings of record have provided any other utilities for the claimed transgenic mice that are specific and substantial. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the transgenic mouse encompassed by the claims. Thus, using the mice claimed for further research is not a "substantial utility".

Applicants argue that the claims, as amended, provide specific utility to the claimed invention, particularly, that the mouse's genome comprises a null chemokine receptor 9A allele, and that the specific polynucleotide for a chemokine receptor 9A allele is disclosed in Figure 1, as SEQ ID NO:1, and that claims 32 and 33 claim a specific phenotype, for the homozygous transgenic mouse of exhibits decreased performance on an accelerating rotarod. See p. 11 of the Response. This is not found to be persuasive. The ranges set forth in Table 1 show overlapping ranges. For example, the first wild-type mouse has a value of 5.96 and the last

wild-type mouse has a value of 11.42; and the knockout mice have values within these ranges. Thus, it is unclear if this is statistically significant when determining the phenotype. Furthermore, the contemplated utilities of the claimed mice are not specific to the chemokine receptor 9A allele, as they are general utilities that can be applied to any knockout mouse. There is no correlation between the phenotypes of the claimed mice and the knockout of the chemokine receptor 9A allele, and thus, the contemplated utilities for these mice are not specific to the invention, and thus, do not have specific utility.

Applicants argue that the mouse has substantial utility, because the specification contemplates using the mice in methods of identifying agents capable of affecting a phenotype of the transgenic animal, methods of identifying agents that have an effect of chemokine 9A expression or function, and that drug discovery and development is a substantial, real world discovery. Applicants cite Shah for support for this. Applicants argue that because a retrospective evaluation of the knockout phenotypes correlate well with known drug efficacy, illuminating a productive path forward for discovering future drug targets, and that compound identification and target gene validation are two real-world, well-established utilities for the transgenic mice of this invention. See pp. 11-12 of the Response.

This is not persuasive. The utility guidelines specifically state that further research is not a "substantial utility":

> [T]he following are examples of situations that require or constitute carrying out further research to identify or

> reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":
>
> A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

In this case, further study of mice would have been required to determine how to use the mouse of Applicants' invention as a model of disease, particularly, because the instant specification fails to disclose any specific disease or condition that is associated with the disruption of a chemokine receptor 9A allele. Further, note that it is clear from all of the art provided by Applicants that knockout mice are used to elucidate gene function, which is not considered a substantial utility.

Applicants argue that the mouse of the instant invention is analogous to a gas chromatograph because it is a well-defined system, the transgenic phenotypes are compared directly to a wild-type mouse with same genetic background, and the transgenic mouse is highly specific to the chemokine receptor 9A null allele. Thus, Applicants argue that that a transgenic mouse is designed to test compounds and environmental conditions which affect expression or function of the gene product; and thus, the mouse is a tool to test the functions of a gene, much as the gas chromatograph is used to test the presence of a single compound. See p. 12-13 of the Response.

This is not persuasive. It is reiterated that a gas chromatograph is a research tool with a well-defined function and highly specific use that does not necessitate

further study of itself. It may be that a gas chromatograph may be used for a wide variety of analyses; however, this does not change its specific use for analyzing a sample. In contrast, the claimed invention is not a general tool for analyzing other samples and, at most, serves to study the function of a single gene. In this respect, the utility of a knockout mouse cannot be compared to a gas chromatograph.

Applicants argue that Table 1 , is statistically significant because the 1-p value vs. wild-type controls = 0.99 for rotarod trial 3, and since the only difference between wild-type control mice and the homozygous knockout mice is the mutation, this phenotype is correlated to the knockout of the chemokine 9A receptor allele. See p. 13 of the Response. This is not persuasive. The arguments of counsel cannot take the place of evidence in the record. See *In re* Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965) and MPEP §716.01. Applicants have not provided an appropriate affidavit or declaration supporting that this statistical significance, namely the l-p value = 0.99. Furthermore, there is no evidence of record to show that the wild-type control mice are the same genetic background as the homozygous mice. The specification merely teaches that the mice are age- and gender-matched, but is silent with regard to the genotype of the control mice. This is germane to the instant case because of the strain differences between mice (see prior Office actions, particularly Rustay *et al.*).

Applicants argue that, "at least 13 patents have issues which describe methods for gene function determination or manipulation." See p. 14 of the

Response. This is not persuasive. Each case is prosecuted on its own merits, the instant case at hand fails to have utility, for reasons set forth above and in prior Office actions. It is clear that from the art provided by Applicants, that the knockout mice are used to elucidate gene function, which is not considered a substantial utility.

Applicants argue that there is a statistically significant correlation disclosed in the specification between the claimed phenotypes and knockout of the chemokine receptor 9A gene, and point to pp. 50-51 of the specification, as well Meucci *et al.*, who found that hippocampal neurons contain various types of chemokine receptors, and then Applicants point to the specification to show that chemokines bind to specific cell-surface receptors, and that papers filed since the time of filing have implicated chemokine 9A (CCR9) in multiple disease states. Applicants point to Youn *et al.*, who show the activation of CCR9 led to a potent cFLIP(L) independent resistance to cycloheximide-induced apoptosis, and that CCR9-mediated antiapoptosis could be a framework for cell survival mechanisms. Further, Applicants state that various disease states mediated by CCR9 include, for example, acute and chronic lympocytic leukemia, metastasis of the small intestine. See pp. 14-15 of the Response. Thus, Applicants conclude that the CCR9 mice of the instant invention have substantial and specific utility.

This is not persuasive. The mice of the instantly claimed invention exhibit a phenotype of decreased performance on an accelerating rotarod. It is unclear how

this phenotype is correlated to any of the other disease states that CCR9 is implicated in, for example, leukemia, or cancer. The mice of the instantly claimed invention do not exhibit any phenotypes of diseases that are associated with the expression (or lack of) CCR9. For example, Youn teach the activation of CCR9. The instant invention is directed to the lack of expression of the CCR9A allele. Applicants' arguments are not correlative to the instantly claimed invention because they fail to provide any nexus between the observed phenotypes and the knockout of the CCR9 allele. Thus, the mice fail to have specific or substantial utility for these reasons and those stated in prior Office actions and above. Accordingly, it is maintained that neither specification, nor the art of record provides evidence of the existence of a correlation between decreased agility, coordination or balance and a disease or disorder, leaving the skilled artisan to speculate and investigate the uses of the transgenic mouse encompassed by the claims. The specification essentially provides an invitation to experiment, wherein the artisan is invited to elaborate a functional use for the transgenic mouse encompassed by the claim. Thus, the skilled artisan would not find the asserted utility of the claimed transgenic mice to be specific and substantial.

Claims 31-34, 38 and 40-43 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons

set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Applicants argue traverse the prior rejection and argue that both the method of providing the transgenic mouse and methods of using the mouse in rotarod testing to identify agents capable of modifying the effect of the null allele are clearly

disclosed in the instant invention. Furthermore, Applicants argue that the rejection, which states that behavioral tests are strain-dependent and subject to the hitchhiking effect, that the instantly claimed mice were compared with age- and gender-matched wild-type control mice of the same generational background, and thus, the claimed mice and the control mice have the same identical backgrounds. With regard to the background affect, Applicants argue that the mice used were of uniform background, as the claims are relative to wild-type control mice. See p. 16 of the Response.

This is not persuasive. Careful inspection of the specification reveals that the mice were compared to age- and gender-matched control mice. There is no indication that these mice are of the same generational background, or that they have the same genetic background as the instantly clamed mice. . The arguments of counsel cannot take the place of evidence in the record. See *In re* Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965) and MPEP §716.01. Applicants have not provided an appropriate affidavit or declaration supporting that the mice are compared to mice with identical genetic backgrounds. Furthermore, as stated in the prior Office action, Gerlai teach that wild-type littermates are not good controls for the null mice (page 178, col. 1, lines 6-18).

Applicants argue that the analyses set forth in the specification are not based upon a single mouse, but that the behavioral tests were performed in at least 10 homozygous mice, and compared with at least 10 wild-type control mice; and that

the data underlying these results, including the number of mice, are set forth in DeltaBase. Furthermore, Applicants argue that because all of the employees and consultants in Deltagen's pathology group hold higher degrees, unless the Examiner has reason to doubt the credibility of these reported results, the burden remains on the Exmainer to set forth a *prima facie* case. See pp. 16-17 of the Response. Applicants argue that hitchhiker alleles are not relevant in this situation because the results are not based upon a single mouse, and that thus, an outlier due to the combination of alleles and the KO gene would not be reported as a significant phenotype.

The Examiner has set forth reasons in the prior Office actions as to why the instantly claimed mice lack enablement. Namely, the claimed invention is not enabling because of the observed, and art-recognized hitchhiking effect, wherein it is unclear if the behavioral and physiological effects observed in the presently claimed chemokine receptor 9A null mice could be due to 129/ SvEv genes (see Gerlai, page 179, col. 1, lines 9-14). There is no way to tell given the tests in the disclosure. Thus, determining whether or not the phenotype of the mice seen is due to disrupted gene, the 129 "hitchhiking" alleles or compensation by other C57Bl genes cannot be determined from applicant's data.

It is maintained that there is no enabled use for the claimed mice as the phenotypes disclosed and claimed for the mice are not predictably correlated to the function of the chemokine receptor 9A gene, as taught by the art, and mice are not

taught to have a phenotype that correlates to any disease or condition. No other uses of the mice are disclosed. Finally, as amended, certain of the claims fail to provide an appropriate phenotype for the claimed mice; thus, without an appropriate phenotype, one of skill in the art would not know how to use these claimed mice. Note that enablement requires both how to make and how to use the claimed invention. Accordingly, in view of the above and previously recited reasons, the skilled artisan would have been required to engage in an undue amount of experimentation at the time of filing to implement the invention as claimed.

Claims 31-34, 38 and 40-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained for reasons of record advanced in the prior Office action.

Applicants argue that the claims have written description. Applicants argue that the mouse chemokine receptor 9A gene sequence is disclosed in the specification, and that the cited case law is not relevant to the present situation; namely, that Applicants are claiming a mouse with a null mouse chemokine receptor 9A allele, a single species, and not the genus of mammalian chemokine receptor 9A alleles. See p. 18 of the Response

This is not found to be persuasive. The instantly-filed specification defines a gene as any DNA sequence that encodes a particular amino acid sequence and/or any other DNA sequence that hybridizes to the complement of the coding sequences disclosed in the specification. Thus, the specification has described the nucleotide sequence encoding CCR9 gene, as set forth by SEQ ID NO: 1. However, the genus of CCR9 genes encompassed by the claims, including those that hybridize to the complement of this sequence, lack a written description. The instant specification does not describe what other DNA molecules, other than SEQ ID NO: 1, fall into this genus. Therefore, one could not have envisioned the primary structure of other nucleotides encoding the gene. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics, Inc.*, 48 USPQ2d 1641,1646 (1998).

With the exception of the sequence referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. In view of the above considerations one of skill in the art would not

recognize that applicant was in possession of the necessary common features or attributes possessed by any member of the genus of chemokine receptor 9Agenes other than that set forth by SEQ ID NO:1. Therefore, only the chemokine receptor 9Agene encompassed by SEQ ID NO:1, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 USC § 112

The prior rejection of claims 34 and 38 under 35 U.S.C. 112, second paragraph, is withdrawn in view of Applicants' amendments to the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 31, 34, 38, 40, 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi *et al.* when taken with Zaballos *et al* as evidenced by Genbank Accession Number: NM_009913. This rejection is maintained for reasons of record.

Applicants argue that, as a preliminary matter, Applicants question how the Examiner can argue that requisite motivation exists to create the claimed invention, and yet the Examiner argues that there is no patentable utility and that one skilled in the art would not know how to use the claimed invention. See p. 19 of the Response.

The Examiner asserts that a reference can anticipate an invention without the reference teaching how to use it, within the meaning of 35 U.S.C. §101. See also *In re Schoenwald*, 22 USPQ2d 1671 (CA FC 1992). Thus, the combination of Capecchi and Zaballos is found to be proper and is maintained for reasons of record.

Applicants argue that the cited references, neither alone or in combination, teach or suggest the claimed invention, because the Examiner has not cited any evidence in the references that the particular gene, CCR9, is disrupted. Moreover, one of ordinary skill in the art would not have a resomable expectation of success in making the claimed invention, because Zaballos discloses the mouse chemokine receptor 9A cDNA, and Capecchi requires knowledge of the genomic sequence and restriction mapping to create the targeting vector; therefore, one of skill in the art would have no reasonable expectation of arriving at the claimed invention. See pp. 19-20 of the Response.

This is not persuasive. In fact, Applicants state that, "In fact, knowledge of the sequence of the mouse chemokine receptor 9A gene is not even required to make the knockout mouse." See p. 18, 3rd paragraph of the Response. It is acknowledged

that Zaballos teach a cDNA sequence, but there is no specific teaching in Capecchi that genomic DNA is a required component. Indeed, as supported by Applicants, that the sequence of the gene is not even required to make the knockout mouse; the specification teaches that homologous recombination can occur using homologous DNA, which has varying degrees of sequence identity to the target gene. Thus, because Capecchi teaches methods of homologous recombination, and that sequences that are homologous will recombine with each other (see p. 38, 1st full), accordingly, Capecchi does not require specific knowledge of the genomic sequence, but that homologous sequences will also work in the taught methods. Accordingly, it is maintained that the combination of Capecchi and Zaballos, are proper and provide sufficient motivation to arrive at the claimed invention.

Note that absent any phenotypic requirements of the claimed transgenic mice, the combination of the cited prior art is sufficient to make obvious the invention, further note that it would be well-known in the art that the disruption of any gene of interest, at any particular exon would have a reasonable expectation of decreased expression of that particular gene.

Capecchi teaches knockout technology applied to mice, specifically with respect to the disruption of the *Hox*A-3 gene and as a method of producing the same, applies to determining the *in vivo* biological function of any known gene of interest. For example, Capecchi discloses the applicability of gene targeting to many other genes, so that a correlation can be drawn between the malfunctioning

gene to the manifestation of disease [see p. 41, col. 2, 2nd full paragraph]. Capecchi further discloses the essential components of a targeting vector [p. 38, col. 3, and p. 39, col. 1-2], and the steps involved for targeted gene replacement in ES cells as well as in mice [see p. 36-39 and diagrams]. Capecchi differs from the claimed invention in that the targeting construct does not contain flanking nucleotide sequences which homologous recombine with the chemokine receptor 9A gene. However, prior to the time of the claimed invention, Zaballos teach the sequence of the mouse CCR9 gene. This is evidenced by the Genbank Accession Number NM_009913 (which cites Zaballos) and provides the sequence of the CCR9 gene.

Accordingly, in view of the combined teachings, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the knockout technology of Capecchi by use of a targeting vector for the disruption of the known chemokine receptor 9A, gene in a mouse with a reasonable expectation of success. One of ordinary skill would have been sufficiently motivated to make such a modification, as it was an art-recognized goal to determine the physiological role of a gene of interest by the generation of a knockout mouse, as supported by Capecchi who teach that the generation of mouse models will allow for the observation of effect of a knocking out a particular gene on disease phenotypes. See p. 41, 2nd column, 2nd ¶.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tnt
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